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(74) Common Representative: DESHMUKH, Jayadeep, R.; Ranbaxy Laboratories Limited, 600 College Road East, Suite 2100, Princeton, NJ 08540 (US).

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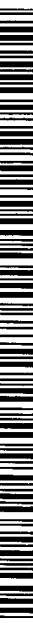
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(71) Applicant (*for all designated States except US*): RANBAXY LABORATORIES LIMITED [IN/IN]; 19, Nehru Place, New Delhi 110 019 (IN).

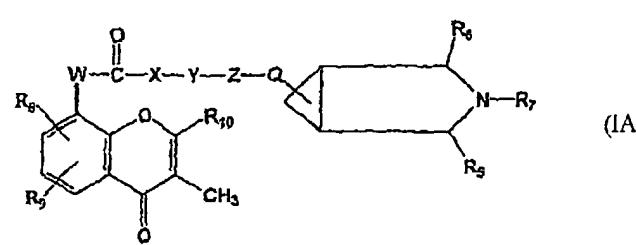
(72) Inventors; and

(75) Inventors/Applicants (*for US only*): MEHTA, Anita [IN/IN]; L-19/3, DLF Qutab Enclave, Phase - II, Gurgaon 122 001, Haryana (IN). SRIVASTAVA, Sanjay, Kumar [IN/IN]; 582, Sector - 17, Gurgaon 122 001, Haryana (IN). GUPTA, Jang, Bahadur [IN/IN]; 349, Sector-14, Gurgaon 122 001, Haryana (IN).



A1

(54) Title: FLAVAXATE DERIVATIVES AS MUSCARINIC RECEPTOR ANTAGONISTS



(57) Abstract: This invention generally relates to the derivatives of 3,6-disubstituted azabicyclo [3.1.0] hexanes of the following formula [IA]. The compounds of this invention can function as muscarinic receptor antagonists, and can be used for the treatment of various diseases of the respiratory, urinary and gastrointestinal systems mediated through muscarinic receptors. The invention also relates to a process for the preparation of the compounds of the present

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invention, pharmaceutical compositions containing the compounds of the present invention and the methods for treating the diseases mediated through muscarinic receptors.

FLAVAXATE DERIVATIVES AS MUSCARINIC RECEPTOR ANTAGONISTS**FIELD OF THE INVENTION**

This invention generally relates to the derivatives of 3,6-disubstituted
5 azabicyclo[3.1.0] hexanes.

The compounds of this invention can function as muscarinic receptor antagonists,
and can be used for the treatment of various diseases of the respiratory, urinary and
gastrointestinal systems mediated through muscarinic receptors.

The invention also relates to a process for the preparation of the compounds of
10 the present invention, pharmaceutical compositions containing the compounds of the
present invention and the methods for treating the diseases mediated through muscarinic
receptors.

BACKGROUND OF THE INVENTION

Muscarinic receptors as members of the G Protein Coupled Receptors (GPCRs)
15 are composed of a family of 5 receptor sub-types (M_1 , M_2 , M_3 , M_4 and M_5) and are
activated by the neurotransmitter acetylcholine. These receptors are widely distributed on
multiple organs and tissues and are critical to the maintenance of central and peripheral
cholinergic neurotransmission. The regional distribution of these receptor sub-types in
the brain and other organs has been documented. For example, the M_1 subtype is located
20 primarily in neuronal tissues such as cerebral cortex and autonomic ganglia, the M_2
subtype is present mainly in the heart where it mediates cholinergically induced
bradycardia, and the M_3 subtype is located predominantly on smooth muscle and salivary
glands (*Nature*, 1986; 323: 411; *Science*, 1987; 237: 527).

A review in *Current Opinions in Chemical Biology*, 1999; 3: 426, as well as in
25 *Trends in Pharmacological Sciences*, 2001; 22: 409 by Eglen et. al., describe the
biological potentials of modulating muscarinic receptor subtypes by ligands in different
disease conditions like Alzheimer's disease, pain, urinary disease condition, chronic
obstructive pulmonary disease etc.

A review in *J. Med. Chem.*, 2000; 43: 4333 by Christian C. Felder et. al.
30 describes therapeutic opportunities for muscarinic receptors in the central nervous

system and elaborates on muscarinic receptor structure and function, pharmacology and their therapeutic uses.

The pharmacological and medical aspects of the muscarinic class of acetylcholine agonists and antagonists are presented in a review in Molecules, 2001, 6: 142.

5 N.J.M. Birdsall et. al. in Trends in Pharmacological Sciences, 2001; 22: 215 have also summarized the recent developments on the role of different muscarinic receptor subtypes using different muscarinic receptors of knock out mice.

10 Muscarinic agonists such as muscarine and pilocarpine and antagonists such as atropine have been known for over a century, but little progress has been made in the discovery of receptor subtype-selective compounds making it difficult to assign specific functions to the individual receptors. Although classical muscarinic antagonists such as atropine are potent bronchodilators, their clinical utility is limited due to high incidence of both peripheral and central adverse effects such as tachycardia, blurred vision, dryness of mouth, constipation, dementia, etc. Subsequent development of the quarterly 15 derivatives of atropine such as ipratropium bromide are better tolerated than parenterally administered options but most of them are not ideal anti-cholinergic bronchodilators due to lack of selectivity for muscarinic receptor sub-types. The existing compounds offer limited therapeutic benefit due to their lack of selectivity resulting in dose limiting side-effects such as thirst, nausea, mydriasis and those associated with the heart such as 20 tachycardia mediated by the M₂ receptor.

Annual review of Pharmacological Toxicol., 2001; 41: 691, describes the pharmacology of the lower urinary tract infections. Although anti muscarinic agents such as oxybutynin and tolterodine that act non-selectively on muscarinic receptors have been used for many years to treat bladder hyperactivity, the clinical effectiveness of these 25 agents has been limited due to the side effects such as dry mouth, blurred vision and constipation. Tolterodine is considered to be generally better tolerated than oxybutynin. (W.D.Steers et. al. in Curr. Opin. Invest. Drugs, 2: 268, C.R. Chapple et. al. in Urology, 55: 33), Steers WD, Barrot DM, Wein AJ, 1996, Voiding dysfunction: diagnosis classification and management. In "Adult and Pediatric Urology," ed. JY Gillenwatter, 30 JT Grayhack, SS Howards, JW Duckett, pp 1220-1325, St. Louis, MO; Mosby. 3rd edition.)

Despite these advances, there remains a need for development of new highly selective muscarinic antagonists which can interact with distinct subtypes, thus avoiding the occurrence of adverse effects.

Compounds having antagonistic activity against muscarinic receptors have been
5 described in Japanese patent application Laid Open Number 92921/1994 and
135958/1994; WO 93/16048; U.S. Patent No. 3,176,019; GB 940,540; EP 0325 571;
WO 98/29402; EP 0801067; EP 0388054; WO 9109013; U.S. Patent No. 5,281,601.
U.S. Patent Nos. 6,174,900, 6,130,232 and 5,948,792; WO 97/45414 are related to
10 1,4-disubstituted piperidine derivatives; WO 98/05641 describes fluorinated,
1,4-disubstituted piperidine derivatives; WO 93/16018 and WO96/33973 are other close
art references.

A report in *J. Med. Chem.*, 2002; 44:984, describes cyclohexylmethyl piperidinyl
triphenylpropioamide derivatives as selective M₃ antagonist discriminating against the
other receptor subtypes.

15

SUMMARY OF THE INVENTION

The present invention provides 3,6-disubstituted azabicyclo[3.1.0]hexanes which function as muscarinic receptor antagonists which are useful as safe treatment of various diseases of the respiratory, urinary and gastrointestinal systems, and method for the synthesis of the compounds.

20

The invention also provides pharmaceutical compositions containing the compounds, and which may also contain acceptable carriers, excipients or diluents which are useful for the treatment of various diseases of respiratory, urinary and gastrointestinal systems.

25

The invention also includes the enantiomers, diastereomers, polymorphs, pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, N-oxides and metabolites of these compounds having the same type of activity.

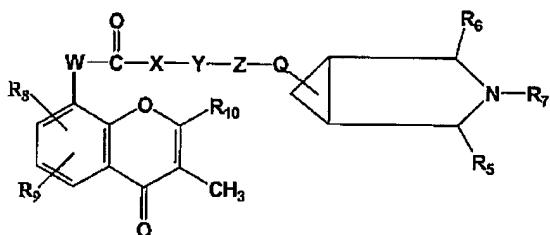
The invention further includes pharmaceutical compositions comprising the compounds of the present invention, their enantiomers, diastereomers, polymorphs,

pharmaceutically acceptable solvates, esters, N-oxides or metabolites, in combination with pharmaceutically acceptable carrier and optionally included excipients.

Other advantages of the invention will be set forth in the description which follows and in part will be apparent from the description or may be learnt by the practice
5 of the invention. The objects and the advantages of the invention may be realized and obtained by means of the mechanisms and combinations pointed out in the appended claims.

In accordance with one aspect of the present invention, there is provided a compound having the structure of Formula I:

10



15

Formula I

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs or metabolites, wherein

- 20 W represents $(CH_2)_p$, where p represents 0 to 1;
- X represents an oxygen, sulphur, -NR or no atom, wherein R represents hydrogen or C_{1-6} alkyl;
- Y represents CHR_1CO , wherein R_1 represents hydrogen, methyl or $(CH_2)_q$ wherein q represents 0 to 4;
- 25 Z represents oxygen, sulphur, NR₂, wherein R₂ represents hydrogen, or C_{1-6} alkyl;
- Q represents $(CH_2)_n$, wherein n represents 0 to 4, or CHR_3 wherein R₃ represents H, OH, C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkoxy or CH_2CHR_4 wherein R₄ represents H, OH, lower alkyl (C_1-C_4) or lower alkoxy (C_1-C_4);

R₅ and R₆ are independently selected from H, COOH, CH₃, CONH₂, NH₂, CH₂NH₂;

- 30 R₇ represents hydrogen, C_1-C_{15} saturated or unsaturated aliphatic hydrocarbon groups in which any 1 to 6 hydrogen atoms may be substituted with the group independently

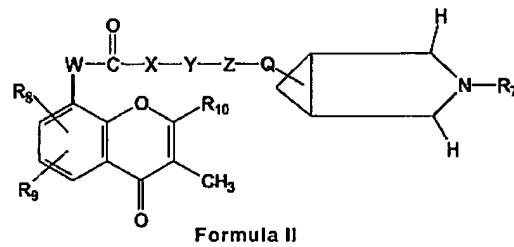
selected from halogen, arylalkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl having 1 to 2 hetero atoms selected from the group consisting of nitrogen, oxygen and sulphur atoms with an option that any 1 to 3 hydrogen atoms on an aryl or heteroaryl ring in said arylalkyl, arylalkenyl, hetero arylalkenyl group may be substituted with lower alkyl (C₁-C₄), lower perhalo alkyl (C₁-C₄), cyano, hydroxyl, nitro, lower alkoxy carbonyl, halogen, lower alkoxy (C₁-C₄), lower perhaloalkoxy (C₁-C₄), unsubstituted amino, N-lower alkylamino (C₁-C₄), N-lower alkylamino carbonyl (C₁-C₄) N,N-lower dialkylamino (C₁-C₄), N,N-lower dialkylaminocarbonyl;

R₈ and R₉ are independently selected from the group consisting of hydrogen, lower alkyl (C₁-C₄), trifluoromethyl, cyano, halogen, hydroxy, nitro, lower alkoxy (C₁-C₄), amino or lower alkylamino; and

R₁₀ represents aryl which may be substituted with one or more substituents.

In accordance with a second aspect of the present invention there is provided a compound having the structure of Formula II and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, metabolites, wherein W, X, Y, Z, Q, R₇, R₈, R₉ and R₁₀ are as defined for Formula I.

20



(Formula I, wherein R₅=R₆=H)

In accordance with a third aspect of the present invention, there is provided a method for treatment or prophylaxis of an animal or a human suffering from a disease or disorder of the respiratory, urinary and gastrointestinal systems, wherein the disease or disorder is mediated through muscarinic receptors, comprising administering to a patient in need thereof, an effective amount of compounds as described above.

In accordance with a fourth aspect of the present invention, there is provided a method for treatment or prophylaxis of an animal or a human suffering from a disease or

disorder associated with muscarinic receptors, comprising administering to a patient in need thereof, an effective amount of compounds as described above.

In accordance with a fifth aspect of the present invention, there is provided a method for treatment or prophylaxis of an animal or a human suffering from a disease or disorder of the respiratory systems such as bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, etc., urinary system which induce such urinary disorders as urinary incontinence, lower urinary tract systems (LUTS), etc., and gastrointestinal system such as irritable bowel syndrome, obesity, diabetes and gastrointestinal hyperkinesis with compound as described above, wherein the disease or disorder is associated with muscarinic receptors, comprising administering to a patient in need thereof, an effective amount of compounds as described above.

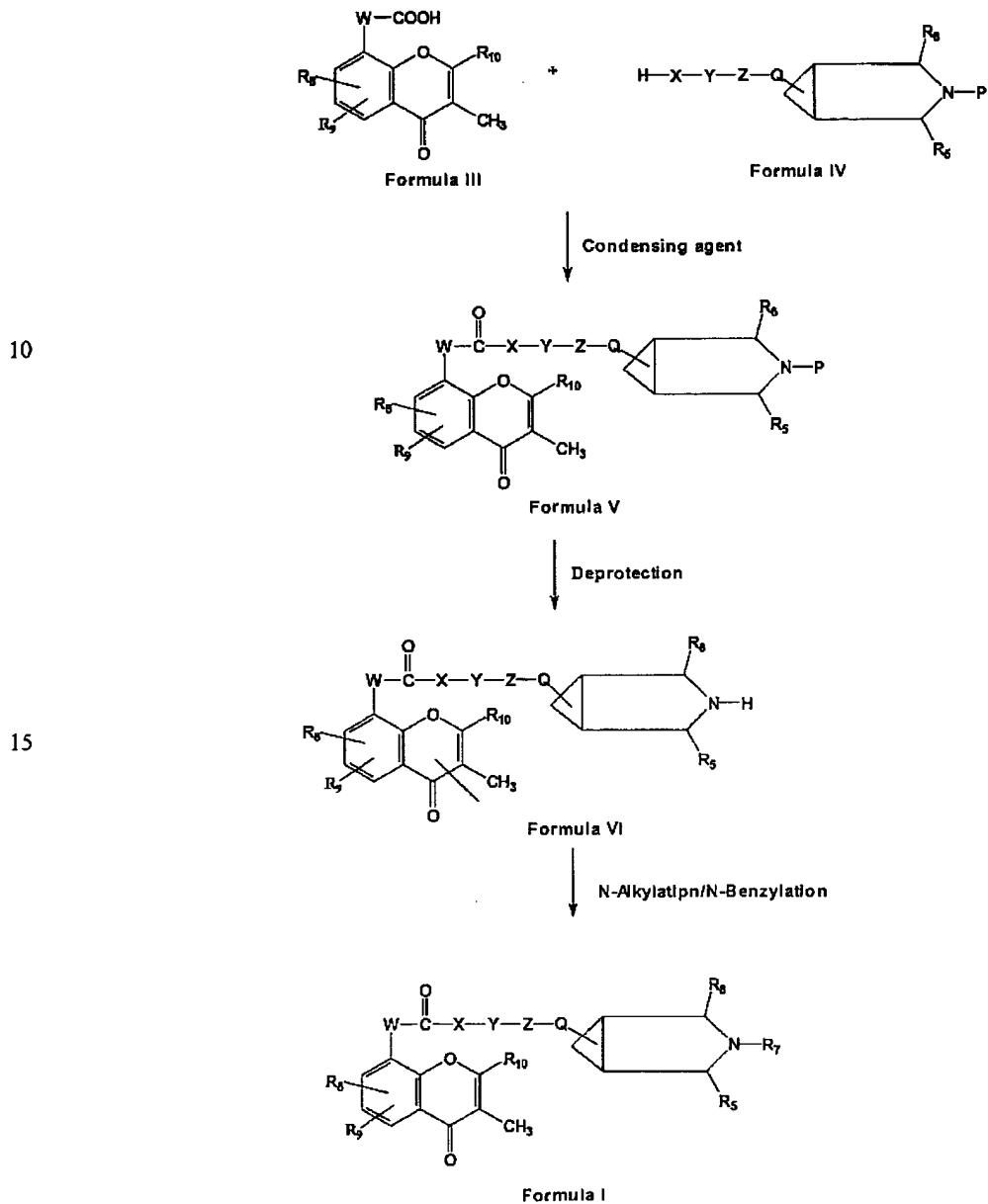
In accordance with a sixth aspect of the present invention, there is provided a process for preparing the compounds as described above.

The compounds of the present invention exhibit significant potency in terms of their activity, which was determined by *in vitro* receptor binding and functional assays and *in vivo* experiments using anaesthetised rabbit. Compounds were tested *in vitro* and *in vivo*. Some compounds were found to function as potent muscarinic receptor antagonists with high affinity towards M₃ receptors. Therefore, the present invention provides pharmaceutical compositions for treatment of diseases or disorders associated with muscarinic receptors. Compounds and compositions described herein can be administered orally or parenterally.

DETAILED DESCRIPTION OF THE INVENTION

The compounds described herein may be prepared by techniques well known in the art and familiar to the average synthetic organic chemist. In addition, the compounds described herein may be prepared by the following reaction sequence:

5

Scheme-I

The compounds of Formula I of the present invention may be prepared by the reaction sequence as shown in Scheme I. The preparation comprises condensing a compound of Formula III with the compound of Formula IV wherein

- 5 W represents $(CH_2)_p$, where p represents 0 to 1;
- X represents an oxygen, sulphur, -NR or no atom, wherin R represents hydrogen or C₁₋₆ alkyl;
- Y represents CHR₁CO, wherein R₁ represents hydrogen, methyl or $(CH_2)^q$ wherein q represents 0 to 4;
- 10 Z represents oxygen, sulphur, NR₂, wherein R₂ represents hydrogen, or C₁₋₆ alkyl;
- Q represents $(CH_2)_n$, wherein n represents 0 to 4, or CHR₃ wherein R₃ represents H, OH, C₁₋₆ alkyl, C₁₋₆ alkenyl, C₁₋₆ alkoxy or CH₂CHR₄ wherein R₄ represents H, OH, lower alkyl (C_{1-C₄}) or lower alkoxy (C_{1-C₄});

R₅ and R₆ are independently selected from H, COOH, CH₃, CONH₂, NH₂, CH₂NH₂;

- 15 R₈ and R₉ are independently selected from hydrogen, lower alkyl (C_{1-C₄}), trifluoromethyl, cyano, hydroxy, nitro, lower alkoxy (C_{1-C₄}), amino or lower alkylamino; and

- P is any group which can be used to protect an amino group in the presence of a condensing agent to give a protected compound of Formula V, which on deprotection through reaction with deprotecting agent in an organic solvent gives an unprotected compound of Formula VI which is finally N-alkylated or benzylated with a suitable alkylating or benzylating agent L-R₇ to give a compound of Formula I, wherein L is any leaving group and

- 25 R₇ represents hydrogen, C_{1-C₁₅} saturated or unsaturated aliphatic hydrocarbon groups in which any 1 to 6 hydrogen atoms may be substituted with the group independently selected from halogen, arylalkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl having 1 to 2 hetero atoms selected from the group consisting of nitrogen, oxygen and sulphur atoms with an option that any 1 to 3 hydrogen atoms on an aryl or heteroaryl ring in said arylalkyl, arylalkenyl, hetero arylalkenyl group may be substituted with lower alkyl (C_{1-C₄}), lower perhalo alkyl (C_{1-C₄}), cyano, hydroxyl, nitro, lower alkoxy carbonyl, halogen,

lower alkoxy (C₁-C₄), lower perhaloalkoxy (C₁-C₄), unsubstituted amino, N-lower alkylamino (C₁-C₄), N-lower alkylamino carbonyl (C₁-C₄), N,N-lower dialkylamino (C₁-C₄), N,N-lower dialkylaminocarboynl.

P is any protecting group for an amino group for a compound of Formula VI and
5 is selected from benzyl and t-butyloxy carbonyl groups.

The reaction of the compound of Formula III with a compound of Formula IV to give a compound of Formula V can be carried out in the presence of a condensing agent, for example 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDC) and 1, 8-diazabicyclo [5.4.0] undec-7ene (DBU).

10 The reaction of the compound of Formula III with a compound of Formula IV to give a compound of Formula V can be carried out in a suitable solvent, for example, N, N-dimethylformamide, dimethylsulfoxide, toluene and xylene at a temperature ranging from about 0 to about 140°C.

15 The deprotection of the compound of Formula V to give a compound of Formula VI can be carried out with a deprotecting agent, for example, palladium on carbon, trifluoroacetic acid (TFA) and hydrochloric acid.

20 The deprotection of the compound of Formula V to give a compound of Formula VI can be carried out in a suitable organic solvent, for example those selected from the group consisting of methanol, ethanol, tetrahydrofuran and acetonitrile at temperatures ranging from about 10 to about 50°C.

The N-alkylation or benzylation of the compound of Formula VI to give a compound of Formula I can be carried out with a suitable alkylating or benzylating agent, L-R₇ wherein L is any leaving group, known in the art, for example, halogen, O-mestyl and O-tosyl group.

25 The N-alkylation or benzylation of the compound of Formula VI to give a compound of Formula I can be carried out in a suitable organic solvent such as N, N-dimethylformamide, dimethylsulfoxide, tetrahydrofuran and acetonitrile at temperature ranging from about 25 to about 100°C.

In the above scheme, where specific bases, condensing agents, protecting groups, deprotecting agents, N-alkylating/benzylating agents, solvents, etc. are mentioned, it is to be understood that other bases, condensing agents, protecting groups, deprotecting agents, N-alkylating/benzylating agents, solvents, etc. known to those skilled in the art 5 may be used. Similarly, the reaction temperature and duration may be adjusted according to the desired needs.

Suitable salts of compounds represented by the Formula I were prepared so as to solubilize the compound in aqueous medium for biological evaluations. Examples of such salts are pharmacologically acceptable salts such as inorganic acid salts (e.g. 10 hydrochloride, hydrobromide, sulphate, nitrate and phosphate), organic acid salts (e.g. acetate, tartarate, citrate, fumarate, maleate, tolounesulphonate and methanesulphonate). When a carboxyl group is included in the Formula I as a substituent, it may be in its alkali metal salt form (e.g. sodium, potassium, calcium, magnesium, and the like). These salts may be prepared by usual prior art techniques, such as treating the compound with 15 an equivalent amount of inorganic or organic, acid or base in a suitable solvent.

Particular compounds which are capable of being produced by Scheme I include:

Compound No.	Chemical Name
	(1 α , 5 α , 6 α)-6N-[3-benzyl-3-azabicyclo[3.1.0]hexyl]-3-methyl-4-oxo- α -phenyl-4H-1-benzopyran-8-carboxamide (Compound No. 1)
20	(1 α , 5 α , 6 α)-6N-[3-(4-cyanobenzyl)-3-azabicyclo[3.1.0]hexyl]-3-methyl-4-oxo-2-phenyl-4H-1-benzopyran-8-carboxamide (Compound No. 2)
	(1 α , 5 α , 6 α)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-3-methyl-4-oxo-2-phenyl-4H-1-benzopyran-8-carboxamide (Compound No. 3)
25	(1 α , 5 α , 6 α)-N-[3-(4-methyl-3-pentyl)-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-3-methyl-4-oxo-2-phenyl-4H-1-benzopyran-8-carboxamide (Compound No. 4)
	N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-1-(aminomethyl)-yl]-3-methyl-4-oxo-2-phenyl-4H-1-benzopyran-8-carboxamide (Compound No. 5)

Compounds or compositions disclosed herein may be administered to an animal for treatment orally, or by a parenteral route. Pharmaceutical compositions disclosed 30 here can be produced and administered in dosage units, each unit containing a certain

amount of at least one compound described herein and/or at least one physiologically acceptable salt addition thereof. The dosage may be varied over extremely wide limits as the compounds are effective at low dosage levels and relatively free of toxicity. The compounds may be administered in the low micromolar concentration, which is
5 therapeutically effective, and the dosage may be increased as desired up to the maximum dosage tolerated by the patient.

The present invention also includes the enantiomers, diastereomers, N-Oxides, polymorphs, solvates and pharmaceutically acceptable salts of these compounds as well as metabolites having the same type of activity. The present invention further includes
10 pharmaceutical composition comprising the molecules of Formula I and II, or prodrugs, metabolites, enantiomers, diastereomers, N-oxides, polymorphs, solvates or pharmaceutically acceptable salts thereof, in combination with pharmaceutically acceptable carrier and optionally included excipients.

The examples mentioned below demonstrate the general synthetic procedure as
15 well as the specific preparation of the preferred compound. The examples are provided to illustrate the particular aspects of the disclosure and should not be constrained to limit the scope of the present invention, as defined by the claims.

EXAMPLES

Various solvents, such as acetone, methanol, pyridine, ether, tetrahydrofuran,
20 hexanes, and dichloromethane were dried using various drying reagents according to the procedures well known in the literature. 1R spectra were recorded as nujol mulls or a thin neat film on a Perkin Elmer Paragon instrument, Nuclear Magnetic Resonance (NMR) spectra were recorded on a Varian XL-300 MHz instrument using tetramethylsilane as an internal standard.

25 Example 1: Synthesis of (1 α , 5 α , 6 α)-6N-[3-benzyl-3-azabicyclo[3.1.0]hexyl]-3methyl-4-oxo-2-phenyl-4H-1-benzopyran-8-carboxamide (Compound No. 1)

Step a: Synthesis of monoprotected (1 α , 5 α , 6 α)-6-amino-3-azabicyclo[3.1.0]hexane

The compound monoprotected (1 α , 5 α , 6 α)-6-amino-3-azabicyclo[3.1.0] hexane

was synthesized following the procedure of T.F. Braish et al., Synlett, 1996, 1100.

Step b: Synthesis of (1 α , 5 α , 6 α)-6N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-3methyl-4-oxo-2-phenyl-4H-1-benzopyran-8-carboxamide

A solution of flavone-3-carboxylic acid which was available commercially from
5 Lancaster (1 mmol) and monoprotected (1 α , 5 α , 6 α)-6-amino-3-azabicyclo[3.1.0]hexane
(1.5 mmol) in DMF was cooled to 0°C. 1-Hydorxy benzotriazole (1.2mmol) was added
to the reaction mixture (RM) followed by the addition of N-methylmorpholine (1 mmol)
and the reaction mixture was stirred for 30 minutes. 1-(3-dimethylaminopropyl)-3-ethyl
carbodimide hydrochloride was added and the reaction mixture was stirred for 3 hrs at
10 0°C followed by stirring at RT for overnight. The RM was poured into water and
extracted with ethyl acetate. The organic layer was dried and the residue obtained after
removal of solvents was used as such.

mp = 182-184°C,

IR(KBr):3287, 2276, 1635 cm⁻¹,

15 ¹H NMR δ values: 8.48-8.45 (m, 1H), 8.37-8.35 (m,1H), 7.65-7.63 (m,5H), 7.58-7.57
(m,1H), 7.32-7.22 (m,5H), 3.58 (s, 2H), 3.33 (m,1H), 3.12 (d, 2H, J = 9.0 Hz), 2.40 (d,
2H, J = 9.0 Hz), 2.18 (s, 3H), 1.74 (bs, 1H), 1.43 (m, 2H);
Mass (m/z) = 451.2.

Example 2: Synthesis of (1 α , 5 α , 6 α)-6N-[3-(4-cyanobenzyl)-3-
20 azabiacyclo[3.1.0]hexyl]-3-methyl-4-oxo-2phenyl-4H-1-benzopyran-8-carboxamide
(Compound No. 2)

Step a: The title compound of Example 1 was added to a suspension of 10% palladium
on carbon in methanol and the RM stirred at room temperature for 10 hours under
hydrogen atmosphere. The RM was filtered over celite. The residue obtained after
25 removal of solvent was used as such in the next step.

**Step b: Synthesis of (1 α , 5 α , 6 α)-6N-[3-(4-cyanobenzyl)-3-azabicyclo [3.1.0] hexyl]-3-
methyl-4-oxo-2-phenyl-4H-1-benzopyran-8-carboxamide**

A solution of the compound prepared in step a (1 mmol), 4-cyano benzoylbromide (1.2
30 mmol), potassium carbonate (8 mmol) and potassium iodide (2 mmol) in DMF (10ml)
was stirred at room temperature for 48 hours. The RM was poured into water and
extracted with ethyl acetate. The organic layer was dried and the residue obtained after

removal of the solvent was purified by column chromatography (100-200 mesh silicagel), eluting the product with 70% ethyl acetate - hexane mixture.

m.p:213-215°C;

IR (KBr):3281, 2221, 1639 cm⁻¹;

- 5 ¹H NMR δ values: 8.852-8.49 (m, 1H), 8.41-8.38 (m, 1H), 7.65-7.36 (m, 10H), 3.62 (s, 2H), 3.31 (m, 1H) 3.11 (d, 2H, J = 9.0 Hz), 2.40 (d, 2H, J = 9Hz), 2.29 (s, 3H), 1.44 (m, 2H); Mass(m/z) = 476

Example 3: Synthesis of (1α, 5α, 6α)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-3-methyl-4-oxo-2-phenyl-4H-1-benzopyran-8-carboxamide

- 10 (Compound No. 3)

Step a: Synthesis of monoprotected (1α, 5α, 6α)-6-aminomethyl-3-benzyl-3-azabicyclo[3.1.0]hexane

The compound monoprotected (1α, 5α, 6α)-6-aminomethyl-3-benzyl-3-azabicyclo[3.1.0]hexane was synthesised as per the procedure of EP 0413455A2.

- 15 Step b: Synthesis of monoprotected (1α, 5α, 6α)-N-[3-benzyl]-3-azabicyclo[3.1.0]hexyl 6-amino methyl-yl)-3methyl-4-oxo-2-phenyl-4H-1-benzo-8-carboxamide

This compound was synthesized following the procedure as in Example 1, step-b using
20 (1α, 5α, 6α)-6-aminomethyl-3-benzyl-3-azabicyclo[3.1.0]hexane instead of (1α, 5α, 6α)-6-amino-3-azabicyclo[3.1.0]hexane. The compound was purified by column chromatography 100-200 mesh size silicagel), eluting the compound with 70% ethyl acetate-hexane mixture.

m.p = 175-177°C

- 25 IR(KBr): 3293, 2921, 1645 cm⁻¹,

¹H NMR δ values: 8.852-8.559 (m, 1H), 8.41-8.44 (m, 1H), 7.53-7.70 (m, 6H), 5.12 (m, 1H), 3.17-3.25 (m, 3H), 2.36-2.43 (m, 4H), 2.23 (s, 3H), 2.12-2.17 (m, 2H), 1.61-1.71 (m, 6H), 1.45 (m, 2H)

Mass m/z = 443.2

Example 4: Synthesis of ($1\alpha, 5\alpha, 6\alpha$)-N-[3-[4-methyl-3-pentenyl]-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-3-methyl-4-oxo-2-phenyl-4H-1-benzo-pyran-8-carboxamide (Compound No 4)

Step a: Synthesis of ($1\alpha, 5\alpha, 6\alpha$)-N-[3-azabicyclo [3.1.0]hexyl-6-(aminomethyl)-yl]-

5 **3-methyl-4-oxo-2-phenyl-4H-benzo-8-carboxamide**

The compound ($1\alpha, 5\alpha, 6\alpha$)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-3-methyl-4-oxo-2-phenyl-4H-1-benzopyran-8-carboxamide was added to a suspension of 10% Pd-C in methanol and the reaction mixture was stirred at room temperature for 10 hr under hydrogen atmosphere. The reaction mixture was filtered over celite pad. The 10 residue obtained after the removal of solvents was used as such in the next step.

Step b: Synthesis of ($1\alpha, 5\alpha, 6\alpha$)-6N-[3-(4-methyl-3-pentenyl)-3-azabicyclo[3.1.0]hexyl]-3-methyl-4-oxo-2-phenyl-4H-1-benzopyran-8-carboxamide

A solution of the compound prepared in step a (1 mmol), 4-methyl-3-pentenoyl bromide (1.2 mmol), potassium carbonate (8 mmol) and potassium iodide (2 mmol) in DMF 15 (10ml) was stirred at room temperature for 48 hours. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was dried and the residue obtained after removal of the solvent was purified by column chromatography (100-200 mesh silicagel), eluting the product with 70% ethyl acetate - hexane mixture.

m.p: 125-127°C;

20 IR (KBr): 3310, 2832, 1641 cm^{-1} ;

^1H NMR δ values: 8.41-8.38 (m, 1H), 8.35-8.32 (m, 1H), 7.66-7.64 (m, 2H), 7.54-7.43 (m, 4H), 7.31-7.25 (m, 5H), 3.54 (s, 2H), 3.30-3.26 (m, 2H), 2.74 (d, 2H, $J = 9$ Hz), 2.24-2.17 (m, 5H), 1.41 (bs, 1H), 1.19 (m, 2H);

Mass m/z = (465.1)

25 Example 5: Synthesis of N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-1-(amino methyl)-yl]-3-methyl-4-oxo-2-phenyl-4H-1-benzo-8-carboxamide. (Compound No. 5)

Step a: Synthesis of 1-aminomethyl-3-benzyl-3-azabicyclo[3.1.0]hexane.

The compound was synthesized following the procedure described in EP 0413 4 55A2

Step b: Synthesis of N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-1-(aminomethyl)-3-methyl-4-oxo-2-phenyl-4H-1-benzo-8-carboxamide.

A solution of flavone-8-carboxylic acid (1mmol) which was available commercially from 5 Lancaster and monoprotected ($1\alpha, 5\alpha, 6\alpha$)-6-amino-3-azabicyclo [3.1.0] hexane which was synthesized following the procedure of T.F. Braish et al., *Synlett*, 1996, 1100. (1.5mmol) in dimethylformamide was cooled to 0°C. 1-hydroxy benzotriazole(1.2 mmol) followed by N-methyl morpholine (1mmol) was added to the reaction mixture and stirred for 30 minutes. 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide 10 hydrochloride was added and the reaction mixture was stirred for 3 hr. at 0°C followed by stirring at room temperature for overnight. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was dried and the semisolid obtained after the removal of the solvent was used as such.

IR (KBr):3445, 2788, 1636cm⁻¹;

15 ^1H (NMR): 8.42-8.54 (m, 2H), 7.49-7.63 (m, 6H), 7.22-7.32 (m, 5H), 3.76 (m, 1H), 3.49 (s, 2H), 3.35-3.37 (m, 1H), 2.82-2.85 (m, 1H), 2.72-2.75 (m, 1H) 2.16-2.25 (m, 5H), 1.12-1.26 (m, 1H), 0.89-0.91 (m, 1H), 0.27-0.29 (m, 1H);

Mass (m/z) = 465.2.

20 Example 6: Biological Activity

Radioligand Binding Assays:

The affinity of test compounds for M₂ and M₃ muscarinic receptor subtypes was determined by [³H]-N-methylscopolamine binding studies using rat heart and submandibular gland respectively as described by Moriya et al., (*Life Sci*, 1999,64(25):2351-2358) with minor modifications.

Membrane preparation: Submandibular glands and heart were isolated and placed in ice cold homogenising buffer (HEPES 20mM, 10mM EDTA, pH 7.4) immediately after sacrifice. The tissues were homogenised in 10 volumes of homogenising buffer and the homogenate was filtered through two layers of wet gauze and filtrate was centrifuged at

500g for 10min. The supernatant was subsequently centrifuged at 40,000g for 20 min. The pellet thus obtained was resuspended in same volume of assay buffer (HEPES 20 mM, EDTA 5mM, pH 7.4) and were stored at -70°C until the time of assay.

- Ligand binding assay:** The compounds were dissolved and diluted in DMSO. The 5 membrane homogenates (150-250 µg protein) were incubated in 250 µl of assay buffer (HEPES 20 mM, pH 7.4) at 24-25°C for 3h. Non-specific binding was determined in the presence of 1 µM atropine . The incubation was terminated by vacuum filtration over GF/B fiber filters(Wallac). The filters were then washed with ice cold 50mM Tris HCl buffer (pH 7.4). The filter mats were dried and bound radioactivity retained on filters was 10 counted. The IC₅₀ & Kd were estimated by using the non-linear curve fitting program using G Pad Prism software. The value of inhibition constant Ki was calculated from competitive binding studies by using Cheng & Prusoff equation (*Biochem Pharmacol*, 1973,22: 3099-3108), $Ki = IC_{50} / (1+L/Kd)$, where L is the concentration of [³H]NMS used in the particular experiment. pki is - [log Ki].
- 15 The results of the in-vitro tests are listed in Tables I.

Table - I

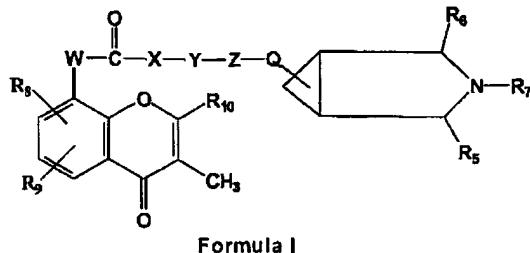
Receptor Binding Assay		
Compound No. 1	M ₂ pki	M ₃ pki
	< 5	< 5
Compound No. 2	< 5	< 5
Compound No. 3	<5.3	5.1
Compound No. 4	<6	<6
Compound No. 5	<6	<6
Tolterodine	8.3	8.13

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in 20 the art and are intended to be included within the scope of the present invention.

WE CLAIM:

1. A compound having the structure of Formula I:

5



and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, metabolites wherein

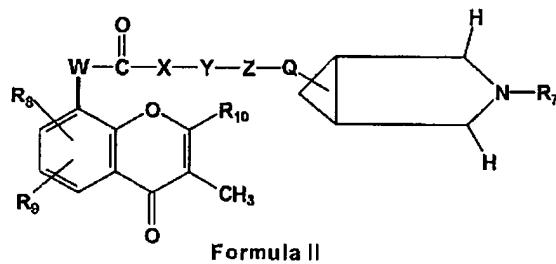
- W represents $(\text{CH}_2)_p$, where p represents 0 to 1;
- 10 X represents an oxygen, sulphur, -NR or no atom wherein R represents hydrogen or C_{1-6} alkyl;
- Y represents CHR_1CO , wherein R_1 represents hydrogen or methyl or $(\text{CH}_2)_q$ wherein q represents 0 to 4;
- Z represents oxygen, sulphur, NR₂, wherein R₂ represents hydrogen, or C_{1-6} alkyl;
- 15 Q represents $(\text{CH}_2)_n$ wherein n represents 0 to 4, or CHR_3 wherein R₃ represents H, OH, C_{1-6} alkyl, C_{1-6} alkenyl C_{1-6} alkoxy or CH_2CHR_4 wherein R₄ represents H, OH, lower alkyl (C_{1-C_4}) or lower alkoxy (C_{1-C_4});
- R₅ and R₆ are independently selected from COOH, H, CH₃, CONH₂, NH₂, CH₂NH₂;
- 20 R₇ represents hydrogen, $\text{C}_{1-\text{C}_{15}}$ saturated or unsaturated aliphatic hydrocarbon groups in which any 1 to 6 hydrogen atoms may be substituted with the group independently selected from halogen, arylalkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl having 1 to 2 hetero atoms selected from a group consisting of nitrogen, oxygen and sulphur atoms with option that any 1 to 3 hydrogen atoms on an aryl or heteroaryl ring in said arylalkyl, arylalkenyl, hetero arylalkenyl group may be substituted with lower alkyl (C_{1-C_4}), lower perhalo alkyl (C_{1-C_4}), cyano, hydroxyl, nitro, lower alkoxy carbonyl, halogen, lower alkoxy (C_{1-C_4}), lower perhaloalkoxy (C_{1-C_4}); unsubstituted amino, N-lower alkylamino (C_{1-C_4}), N-lower alkylamino carbonyl (C_{1-C_4}), N,N-lower dialkylamino (C_{1-C_4}), N,N-lower dialkylaminocarbonyl;
- 25

R_8 and R_9 are independently selected from the group consisting of hydrogen, lower alkyl (C_1-C_4), trifluoromethyl, cyano, hydroxy, nitro, lower alkoxy (C_1-C_4), amino or lower alkylamino; and

R_{10} represents aryl which may be substituted with one or more substituent.

- 5 2. The compound according to claim 1 having the structure of Formula II and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, metabolites wherein R_8 , R_9 , R_{10} , R_7 , W , X , Y , Z , Q are the same as defined for Formula I

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(Formula I, wherein $R_5=R_6=H$)

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3. A compound selected from the group consisting of:
- (1α , 5α , 6α)- $6N$ -[3-benzyl-3-azabicyclo[3.1.0]hexyl]-3-methyl-4-oxo- α -phenyl-4H-1-benzopyran-8-carboxamide (Compound No. 1)

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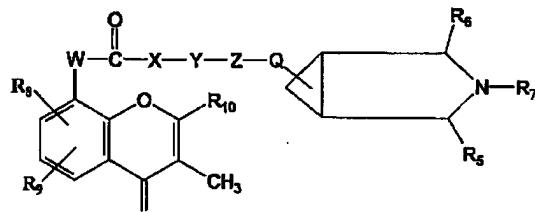
(1α , 5α , 6α)- $6N$ -[3-(4-cyanobenzyl)-3-azabicyclo[3.1.0]hexyl]-3-methyl-4-oxo-2-phenyl-4H-1-benzopyran-8-carboxamide (Compound No. 2)

($1\alpha, 5\alpha$, 6α)- N -[3-benzyl-3-azabicyclo [3.1.0] hexyl-6-(aminomethyl)-yl]-3-methyl-4-oxo-2-phenyl-4H-1-benzopyran-8-carboxamide (Compound No. 3)

($1\alpha, 5\alpha, 6\alpha$)- N -[3-(4-methyl-3-pentyl)-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-3-methyl-4-oxo-2-phenyl-4H-1-benzopyran-8-carboxamide (Compound No. 4)

N -[3-benzyl-3-azabicyclo[3.1.0]hexyl-1-(aminomethyl)-yl]-3-methyl-4-oxo-2-phenyl-4H-1-benzopyran-8-carboxamide (Compound No. 5)

4. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound as defined in claim 1, 2 or 3 together with pharmaceutically acceptable carriers, excipients, or diluents.
5. A method for treatment or prophylaxis of an animal or a human suffering from a disease or disorder of the respiratory, urinary and gastrointestinal systems, wherein the disease or disorder is mediated through the muscarinic receptors, comprising administering to said animal or human, a therapeutically effective amount of a compound having the structure of Formula I,



Formula I

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or its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, metabolites, wherein:

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W represents $(CH_2)_p$, where p represents 0 to 1;

X represents an oxygen, sulphur, -NR or no atom wherein R represents hydrogen or C₁₋₆ alkyl;

Y represents CHR₁CO, wherein R₁ represents hydrogen or methyl or $(CH_2)_q$ wherein q represents 0 to 4;

Z represents oxygen, sulphur, NR₂, wherein R₂ represents hydrogen, or C₁₋₆ alkyl;

Q represents $(CH_2)_n$ wherein n represents 0 to 4, or CHR₃ wherein R₃ represents H, OH, C₁₋₆ alkyl, C₁₋₆ alkenyl, C₁₋₆ alkoxy or CH₂CHR₄ wherein R₄ represents H, OH, lower alkyl (C_{1-C₄}) or lower alkoxy (C_{1-C₄});

25

R₅ and R₆ are independently selected from COOH, H, CH₃, CONH₂, NH₂, CH₂NH₂;

R₇ represents hydrogen, C_{1-C₁₅} saturated or unsaturated aliphatic hydrocarbon groups in which any 1 to 6 hydrogen atoms may be substituted with the group independently selected from halogen, arylalkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl having 1 to 2 hetero atoms selected from a group consisting of

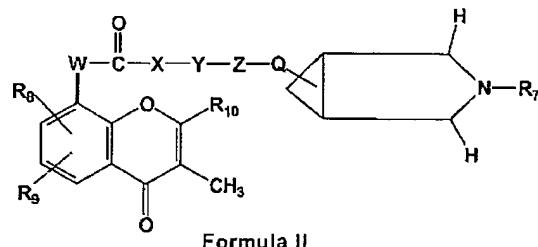
nitrogen, oxygen and sulphur atoms with option that any 1 to 3 hydrogen atoms on an aryl or heteroaryl ring in said arylalkyl, arylalkenyl, hetero arylalkenyl group may be substituted with lower alkyl (C₁-C₄), lower perhalo alkyl (C₁-C₄), cyano, hydroxyl, nitro, lower alkoxy carbonyl, halogen, lower alkoxy (C₁-C₄), lower perhaloalkoxy (C₁-C₄); unsubstituent amino, N-lower alkylamino (C₁-C₄), N-lower alkylamino carbonyl (C₁-C₄), N,N-lower dialkylamino (C₁-C₄), N,N-lower alkylaminocarbonyl;

R₈ and R₉ are independently selected from lower alkyl (C₁-C₄), trifluoromethyl, cyano, hydroxy, nitro, lower alkoxy (C₁-C₄), amino or lower alkylamino; and

R₁₀ represents aryl which may be substituted with one or more substituent.

6. The method according to claim 5 for treatment or prophylaxis of an animal or a human suffering from a disease or disorder of the respiratory, urinary and gastrointestinal systems, wherein the disease or disorder is mediated through the muscarinic receptors, comprising administering to said animal or human, a therapeutically effective amount of a compound having the structure of Formula II, and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, polymorphs, or metabolites, wherein R₈, R₉, R₁₀, R₇, W,X,Y,Z,Q are as defined for Formula I.

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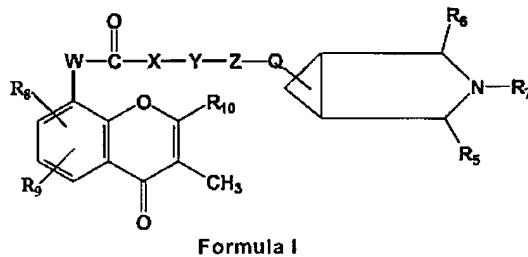
(Formula I, wherein R₅=R₆=H)

7. The method according to claim 5 wherein the disease or disorder is urinary incontinence, lower urinary tract symptoms (LUTS), bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, irritable bowel syndrome, obesity, diabetes, and gastrointestinal hyperkinesia.

8. The method according to claim 6 wherein the disease or disorder is urinary incontinence, lower urinary tract symptoms (LUTS), bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, irritable bowel syndrome, obesity, diabetes, and gastrointestinal hyperkinesis.
- 5 9. The method for treatment or prophylaxis of an animal or a human suffering from a disease or disorder of the respiratory, urinary, and gastrointestinal systems, wherein the disease or disorder is mediated through the muscarinic receptors, comprising administering to said animal or human, a therapeutically effective amount of the pharmaceutical composition according to claim 4.
- 10 10. The method according to claim 9 wherein the disease or disorder is urinary incontinence, lower urinary tract symptoms (LUTS), bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, irritable bowel syndrome, obesity, diabetes, and gastrointestinal hyperkineses.

11. A process of preparing a compound of formula I,

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and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, metabolites, wherein
 20 W represents $(CH_2)_p$, where p represents 0 to 1;
 X represents an oxygen, sulphur, -NH or no atom wherein R represents hydrogen or C_{1-6} alkyl;
 Y represents, CHR_1CO wherein R_1 represents hydrogen or methyl or $(CH_2)_q$
 25 wherein q represents 0 to 4;
 Z represents oxygen, sulfur, NR_2 , wherein R_2 represents hydrogen, or C_{1-6} alkyl;

Q represents $(CH_2)_n$ wherein n represents 0 to 4, or CHR_3 wherein R_3 represents H, OH, C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkoxy or CH_2CHR_4 wherein R_4 represents H, OH, lower alkyl (C_{1-C_4}) or lower alkoxy (C_{1-C_4}); or lower alkoxy (C_{1-C_4});

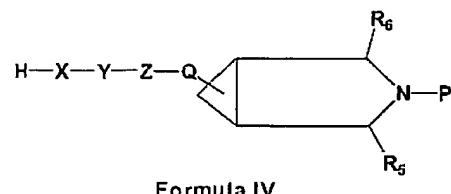
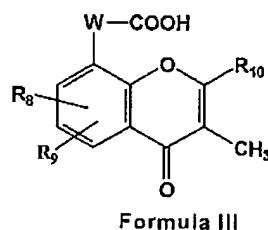
5 R_5 and R_6 are independently selected from COOH, H, CH_3 , CONH₂, NH₂, CH_2NH_2 ;

10 R_7 represents hydrogen, $C_{1-C_{15}}$ saturated or unsaturated aliphatic hydrocarbon groups in which any 1 to 6 hydrogen atoms may be substituted with the group independently selected from halogen, arylalkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl having 1 to 2 hetero atoms selected from a group consisting of nitrogen, oxygen and sulphur atoms with option that any 1 to 3 hydrogen atoms on an aryl or heteroaryl ring in said arylalkyl, arylalkenyl, hetero arylalkenyl group may be substituted with lower alkyl (C_{1-C_4}), lower perhalo alkyl (C_{1-C_4}), cyano, hydroxyl, nitro, lower alkoxy carbonyl, halogen, lower alkoxy (C_{1-C_4}), lower perhaloalkoxy (C_{1-C_4}); unsubstituted amino, N-lower alkylamino (C_{1-C_4}), 15 N-lower alkylamino carbonyl (C_{1-C_4}), N,N-lower dialkylamino (C_{1-C_4}), N,N-lower alkylaminocarbonyl;

R_8 and R_9 are independently selected from lower alkyl (C_{1-C_4}), trifluoromethyl, cyano, hydroxy, nitro, lower alkoxy (C_{1-C_4}), amino or lower alkylamino; and

20 R_{10} represents aryl which may be substituted with one or more substituent, comprising

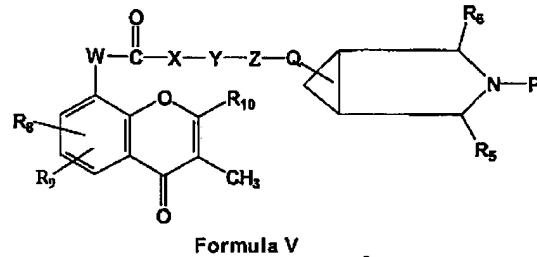
- a) condensing a compound of Formula III with a compound of Formula IV



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wherein W,X,Y,Z, Q, R₁₀, R₇, R₆, R₉, R₈ have the same meanings as defined earlier for Formula I , to give a protected compound of Formula V wherein P is a protecting group for an amino group,

5

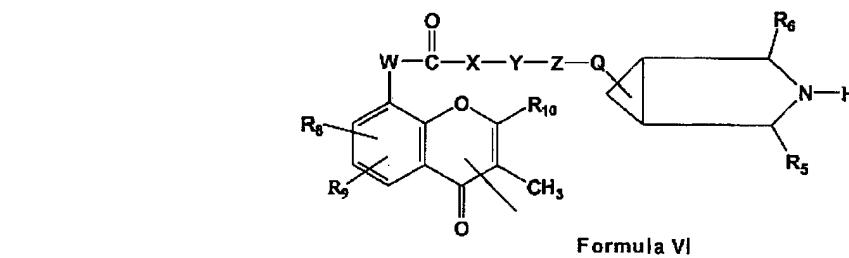


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- b) deprotecting the compound of Formula V in the presence of a deprotecting agent to give an unprotected intermediate of Formula VI wherein R₅,R₆,R₈,R₉,R₁₀, W,X,Y,Z,Q are the same as defined earlier, and

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- c) the intermediate of Formula VI is N-alkylated or benzylated with a suitable alkylating or benzylating agent to give a compound of Formula I wherein R₈,R₉,R₁₀,R₇,R₅, W,X,Y,Z,Q are the same as defined earlier.
- 12. The process according claim 11 wherein P is any protecting group for an amino group and is selected from the group consisting of benzyloxy and t-butyloxy carbonyl groups.
- 13. The process according to claim 11 wherein the reaction of a compound of Formula III with a compound of Formula IV to give a compound of Formula V is carried out in the presence of a condensing agent which is selected from the group consisting of 1-(3-dimethylamino propyl)-3-ethyl carbodiimide hydrochloride (EDC) and 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU).

14. The process according to claim 11 wherein the reaction of a compound of Formula III with a compound of Formula IV to give a compound of Formula V is carried out in the presence of a suitable solvent selected from the group consisting of N,N-dimethylformamide, dimethylsulphoxide, toluene and xylene.
- 5 15. The process according to claim 11 wherein the reaction of a compound of Formula III with a compound of Formula IV is carried out at temperature ranging from about 0-140°C.
- 10 16. The process according to claim 11 wherein the deprotection of a compound of Formula V to give a compound of Formula VI is carried out with a deprotecting agent which is selected from the group consisting of palladium on carbon, trifluoroacetic acid and hydrochloric acid.
- 15 17. The process according to claim 11 wherein the deprotection of a compound of Formula V to give a compound of Formula VI is carried out in a suitable solvent selected from the group consisting of methanol, ethanol, tetrahydrofuran, and acetonitrile.
18. The process according to claim 11 wherein the N alkylation or benzylation of a compound of Formula VI to give a compound of Formula I is carried out with a suitable alkylating or benzylating agent, L-R₇, wherein L is any leaving group and R₇ is the same as defined earlier.

INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/IB 02/05591

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C07D405/12 A61K31/352 A61P13/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 267 319 A (UNITED PHARMACEUTICALS INC) 18 May 1988 (1988-05-18) * see page 10, lines 54-58; page 7, first compound *	1-18
Y	EP 0 108 986 A (HOKURIKU PHARMACEUTICAL) 23 May 1984 (1984-05-23) page 1-4	1-18
Y	EP 0 801 067 A (YAMANOUCHI PHARMA CO LTD) 15 October 1997 (1997-10-15) cited in the application page 3	1-18

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

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- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *&* document member of the same patent family

Date of the actual completion of the International search

16 April 2003

Date of mailing of the International search report

06/05/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3018

Authorized officer

Lauro, P

INTERNATIONAL SEARCH REPORT

Inte	Application No
PCT/IB 02/05591	

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>YUFU SAGARA ET AL.: "Cyclohexylmethylpiperidinyltriphenylpropionamide: a selective muscarinic M3 antagonist discriminating against the other receptor subtypes" J. MED. CHEM., vol. 45, no. 4, 2002, pages 984-987, XP002238502 cited in the application figure 2 ---</p>	1-18
A	<p>EP 0 072 620 A (RECORDATI CHEM PHARM) 23 February 1983 (1983-02-23) the whole document ---</p>	1-18

INTERNATIONAL SEARCH REPORT

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PCT/IB 02/05591	

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